REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested. The IDS is re-submitted herewith. The undersigned apologizes for the citations not being fully listed. The PTO form had a field snafu that prohibited citations over a certain number of characters from being fully displayed, even though the full citation was typed. This error now has been corrected. Copies of the citations already have been submitted. Accordingly, all citations now should be made of record.

The Present Invention

The present invention describes an improved commercial process for the production of carotenoid-cyclodextrin complexes and formulation of the complex for human ingestion. The carotenoids selected include, *inter alia*, lutein, lycopene, meso-zeaxanthin, and a mixture of lutein:zeaxanthin. The cyclodextrins selected from among natural cyclodextrins and their derivatives such as, for example, α-, β-, γ-cyclodextrin, and HP-β-cyclodextrin.

The present invention is based on the unexpected discovery that the commercial method of drying and formulation impacts the ability to retain the high bioavailability of lutein from a lutein-cyclodextrin complex. One of the inventive bioavailable forms is a freeze-dried lutein/γ-cyclodextrin complex formulated in lecithin-vegetable oil or vegetable oil for soft gelatin capsules to be used in the nutritional supplement and pharmaceutical industry. The inventive freeze-dried complex shows a highly significant uptake in *vitro* in Caco2 intestinal cells as compared to, for example, a spray-dried complex described in U.S. Patent Application 10/309,999. The complex on formulation shows a significant uptake *in vitro* in the same model based on the excipients used in formulation.

The present invention also is based on the unexpected discovery that the process can be adapted with modifications to other carotenoids, including, *inter alia*, lycopene and mixtures of carotenoids, such as, for example, lutein and zeaxanthin, and to other cyclodextrins such as, for example, α-, β-, γ-, and hydroxypropyl β-cyclodextrins (HP-β).

The present invention also is based on the unexpected discovery that the *in vitro* uptake of lutein and zeaxanthin from the α-cyclodextrin complex is comparable to the γ-cyclodextrin complex neat.

The invention also discloses simultaneous uptake of stereoisomers lutein and zeaxanthin from cyclodextrin complexes.

The present invention, then, is a method for making a bioavailable carotenoid-cyclodextrin complex for animal ingestion. This method includes commercial production of the complex and

formulating the complex for soft gelatin capsules to retain the properties of the complex. The preferred animal is a human with the route of administration being oral ingestion. The form of the complex for ingestion is a soft gelatin capsule, which may contain other ingredients, both active and inactive. *In vivo*, in a human study, the lutein/γ-cyclodextrin complex improved the absorption of lutein as compared to a commercially available free lutein-oil formulation.

The Claim Rejections

A. Claims 1-10

Claims 1-10 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger (U.S. Patent No. 5,221,735), Fukamachi (U.S. Patent No. 4,929,774), Patel (U.S. Patent No. 6,569,463), Orthoefer (U.S. Patent No. 4,125,630), and copending application serial number 10/309,999 (hereinafter, "USSN '999").

Additionally, claim 9 now stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

B. Claims 11-20

Claims 11-20 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Leuenberger, Fukamachi, Patel, Orthoefer, and USSN '999.

Additionally, claims 4,8,14, and 18 now stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

Additionally, claim 19 now stands rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel in view of USSN '999.

C. Claims 1-3, 5-7, 9-13, 15-17, and 19-20

Claims 1-3, 5-7, 9-13, 15-17, and 19-20 now stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24 of co-pending USSN '999.

D. Claims 1-3, 5-7, 9-13, 15-17, and 19-20

Claims 1-3, 5-7, 9-13, 15-17, and 19-20 now stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over USSN '999.

1. The Previously Cited Art

Leuenberger, Fukamachi, Patael, and Orthoefer were reviewed in detail in Applicant's response of December 21, 2004.

2. Copending Application USSN '999

The declaration of Drs. Madhavi and Kagan accompany this response and should be reviewed in detail. Specifically, Drs. Madhavi and Kagan are two of the 3-named inventors on the USSN '999 application. The declaration affirmatively states that the only contribution of the 3rd named inventor was for certain polymer coatings that were applied to the carotenoid/cyclodextrin complexes. The carotenoid/cyclodextrin complexes themselves were the sole joint invention of Drs. Madhavi and Kagan (¶ 9), as was the preparation of coated carotenoid/cyclodextrin complexes because the complex was unstable as a powder (¶ 10), as was dispersing the carotenoid/cyclodextrin complexes in oil for stability (¶ 12). Thus, any and all disclosure from USSN '999, as cited by the Examiner, was the sole subject matter invented by Drs. Madhavi and Kagan and thus, was not the invention "by another". As such, USSN '999 does not qualify as prior art under the provisions of 35 U.S.C. § 103(a).

Even assuming, *arguendo*, USSN '999 were eligible as prior art, it is totally surprising and unexpected that the method of drying would so dramatically affect the efficiency of recovery of the carotenoid/cyclodextrin complex and the bioavailability of the carotenoid/cyclodextrin complex. USSN '999 only reduces spray drying to practice. Dr. Madhavi's and Dr. Kagan's declaration confirm this fact by stating, *inter alia*, "spray drying was the only drying method studied and actually reduced to practice" (¶ 13 of the Madhavi/Kagan declaration). They further state, *inter alia*, "they had no idea that the method of drying would affect the recovery and bioavailability of the carotenoid/cyclodextrin complexes" (¶ 14 of the Madhavi/Kagan declaration). These statements come from the inventors of the USSN '999 invention and from an admitted expert in the field, Dr. Madhavi. Such statements do not compromise the vitality of the USSN '999 invention; but, they do resound in an understanding or assumption that the USSN '999 inventors had with respect to the method of drying the carotenoid/cyclodextrin product. This fact is accentuated in the laundry list of drying methods set forth in USSN '999. No difference in drying was known to the USSN '999 inventors and only spray drying was reduced to practice.

Despite such teachings in the art, Dr. Madhavi and Dr. Kagan began to test methods of drying of the complex and were astounded to determine that the method of drying dramatically affected the efficiency of recovery of the complex and the bioavailability of the complex. There is no way that the USSN '999 inventors could have known and/or predicted these results without having actually tested different drying methods. Since the USSN '999 inventors did not actually

try (reduce to practice) and compare different drying methods, USSN '999 does not render obvious the surprising and unexpected results now reported in the above-identified application,

While Applicants believe that the foregoing results alone deserve patent protection, there in one more element in claims 1 and 11 that also needs to be discussed—the excipient of choice: "a vegetable oil". USSN '999 discloses coatings, which may be (an oil, a natural polymer or a synthetic polymer." (¶ 012 in USSN '999). The data in Example 5 in the present application compares "freeze-dried lutein/γ-cyclodextrin complex was formulated with medium chain triglycerides (MCT), polysorbate 80, and a combination of lecithin-soybean oil. The formulations were dispersed in PBS and treated with lipase to simulate the digestive process before incorporation into the culture medium." The results reported in Table 5 show both 6-hour and a 24-hour incubation cellular lutein uptake percent increases that are from about 8 to 15 times more uptake at 6 hours and from almost 4 to about 34 times more uptake at 24 hours. Again, while vegetable oil excipients are known in the art, the unexpected bioavailability of freeze-dried carotenoid/cyclodextrin complex with vegetable oil excipients, as set forth in the claims under examination, is not known in the art.

Thus, the present claims are patentable over USSN '999, even were it available as prior art.

3. Combination of Leuenberger, Fukamachi, Patel, Orthoefer, and USSN '999

As an initial matter, the cited combination must technically fail inasmuch as USSN '999 is not eligible to be cited as prior art. Nevertheless, Applicants will address, *arguendo*, such combination below.

The Examiner's criticism of Applicants addressing "each reference individually rather than in the manner that it was used to reject the claims" (*viz.*, combination of references) is not understood. Perhaps, the Examiner should refer to pp. 8-10 of Applicant's prior response under subheading 5, entitled "Combination of Leuenberger, Fukamachi, Patel, and Orthoefer". That 2 plus page discussion does address the combination used to reject the claims. What the Examiner failed to appreciate is that Applicants also took issue with his summary of what each reference teaches; thus, the need to address each reference individually also.

Applicants also take issue with the Examiner's summary dismissal of Dr. Madhavi's declaration "because the showing is not commensurate in scope with the claims" is a glittering generality devoid of substance used to avoid having to address Dr. Madhavi's credentials, statements of facts, and expert opinion. The Examiner has failed to point out what showing is "not commensurate" with the scope of the claims and/or how the claims are broader than the showing in Mr. Madhavi's declaration. In point of fact, both the response and Dr. Madhavi's

declaration address the art combination cited, not merely the references individually. At the risk of being redundant, Applicants will again address the cited art combination.

With respect to the inclusion of a vegetable oil (element (b) of claim 1 and step (c) of claim 11) and the freeze-drying of the complex (element (a) of claim 1 and step (b) of claim 11), Leuenberger describes use of oil to dissolve/disperse carotenoids followed by emulsification with water. Fukamachi describes use of vegetable oils in microencapsulation formulations for oxidation sensitive compounds and mentions lutein and zeaxanthin. However, the oils are used for making an emulsion with the gelatin matrix, an application entirely different from using the oil as an excipient or filler for the cyclodextrin complex, as in the present invention. Orthoefer teaches using triglycerides as plasticizers for making meat analogs from vegetable proteins, again an application entirely different from formulating a carotenoid-cyclodextrin complex into a dosage form as in the present invention. Patel teaches the use of surfactants in the formulation. Again, it is not obvious from these teachings whether a carotenoid cyclodextrin complex can be formulated with these excipients without any adverse effects on the stability of the complex or the bioavailability.

Dr. Madhavi's initial declaration speaks to this issue also. She notes that the weak cyclodextrin/carotenoid bonds can be disrupted by a number of factors, including, *inter alia*, excipients used in formulations, including, *inter alia*, vegetable oils, medium chain triglycerides, and synthetic surfactants such as polysorbates, polyethylene glycols, and phospholipids such as lecithin. She continues that excipients with different polarities may interact with cyclodextrins resulting in the dissociation of the complex, inhibit the release of the actives, or modulate the dissolution properties. The interactions in general are often unpredictable in her expert opinion. Dr. Madhavi cites several publications on the interactions of cyclodextrin inclusion complexes of pharmaceuticals and flavor compounds with formulation excipients. The Examiner has failed to address this expert opinion of Dr. Madhavi with a commensurate showing and has failed to address the numerous additional art cited in Dr. Madhavi's initial declaration. Dr. Madhavi's statements on this issue, then, are unrebutted.

Again, the art combination structured in the claims rejections do not provide the certainty in teaching regarding the vegetable oil portion of the inventive product and process insofar as expected stability of the complex is concerned. The art combination, then, falls far short of rendering unpatentable the present invention.

With respect to the drying method used in forming the complex, Dr. Madhavi emphasizes the data reported in the working examples in the above-identified application. She states that the invention describes a commercially efficient process, which includes freeze-drying an aqueous

dispersion of carotenoid-cyclodextrin complex (step (b) of claim 11 and element (a) of claim 1). Freeze-drying was found to be much more efficient as compared to spray-drying with a 95% recovery of the product with freeze-drying, as compared to 50% recovery (or loss) with spray-drying. Further, to her surprise, the freeze-dried product was superior to spray dried product in bioavailability studies. This unexpectedness is not dispelled or compromised just because freeze-drying is known in the art. The unexpectedness is that for Applicants' product only freeze-drying provided improved bioavailability for the product. Such unexpectedness testifies to the part of of the invention and cannot be predicted. The Examiner is reminded of the data in the working examples in the present application, which contains such bioavailability data for both *in vitro* (Examples 1-4) and *in vivo* (Examples 6 and 7) studies.

Dealing with the soft gel issue, Dr. Madhavi notes that it is well known in the art that hydrophobic compounds present delivery challenges because of their physicochemical properties and soft gelatin capsules may offer a delivery system. However, complexation of carotenoids with cyclodextrins in general resulted in a hydrophilic, water dispersible fine powder. Such complexes are used for making directly compressible tablets or incorporated in to hard gelatin capsules, as cyclodextrins are expected to stabilize sensitive compounds against degradation. However, Dr. Madhavi and her co-inventor found that complexation with cyclodextrins did not stabilize the carotenoids to afford the necessary commercially accepted shelf life in tablets or hard capsules. The soft-gelatin formulation was developed to stabilize the carotenoids. Again, this cannot be predicted and is unexpected.

Dr. Madhavi further states that when hydrophobic excipients, such as vegetable oils, are used, they may inhibit the dispersion of the complex in water; thus, reducing the uptake of the active molecule. However, to her surprise, she found that the complex retained its properties even after formulation with vegetable oil or vegetable oil-lecithin as excipients. Again, the data in Example 5, Table 5, support this statement by Dr. Madhavi.

Dr. Madhavi concludes that in her expert opinion, it was totally unexpected that a commercially feasible, practical, and commercially viable process resulted for making a bioavailable cyclodextrin/carotenoid complex by freeze-drying a cyclodextrin/carotenoid complex in a molar ratio of between about 0.5:1 and 10:1 (element (a) of claim 1), and adding such freeze-dried complex to a vegetable oil (element (b) of claim 1). The art cited simply does not render obvious the present invention in her expert opinion.

4. Summary

In view of the remarks, Rule 132 Declaration of Drs. Madhavi and Kagan, and the remarks herewith, allowance of all claims and passage to issue of this application respectfully is requested.

Respectfully submitted,

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